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Weak evidence on nalmefene creates dilemmas for clinicians and poses questions for regulators and researchers

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ABSTRACT

Background and aims Nalmefene has been approved in Europe for the treatment of alcohol dependence and subsequently recommended by the UK National Institute for Health and Care Excellence (NICE). This study examines critically the evidence base underpinning both decisions and the issues arising. **Methods** Published studies of nalmefene were identified through a systematic search, with documents from the European Medicines Agency, the NICE appraisal and public clinical trial registries also examined to identify methodological issues. **Results** Efficacy data used to support the licensing of nalmefene suffer from risk of bias due to lack of specification of *a priori* outcome measures and sensitivity analyses, use of *post-hoc* sample refinement and the use of inappropriate comparators. Despite this, evidence for the efficacy of nalmefene in reducing alcohol consumption in those with alcohol dependence is, at best, modest, and of uncertain significance to individual patients. The relevance of existing trial data to routine primary care practice is doubtful. **Conclusions** Problems with the registration, design, analysis and reporting of clinical trials of nalmefene did not prevent it being licensed and recommended for treating alcohol dependence. This creates dilemmas for primary care clinicians and commissioning organisations where nalmefene has been heavily promoted, and poses wider questions about the effectiveness of the medicines regulation system and how to develop the alcohol treatment evidence base.

Keywords Addiction, alcohol, brief intervention, nalmefene, trial regulation, vested interests.

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INTRODUCTION

Concerns about the value, analysis and reporting of pharmaceutical industry-sponsored clinical trials are extensive and unresolved [1–8]. Alcohol treatment trials are studies that can be characterized by complexity operating at multiple levels, including trial design and implementation, the nature of the problems and populations targeted, the interventions themselves and their delivery in different health-care settings and systems. Systematic reviews of pharmacotherapies identify few studies at low risk of bias [9], and it has been recommended that guidance available in the wider clinical trials design literature on issues such as recruitment, randomization, statistical methods and outcome evaluation be used more effectively [10]. Problems intrinsic to this area of study are compounded by problems in reporting, where adherence to Consolidated Standards of Reporting Trials (CONSORT) recommendations is weak [11,12]. Conflicting evidence results, for example, with large, apparently well-conducted trials producing findings that are disappointing in light of earlier studies [13]. This makes valid interpretation and use of the evidence base challenging.

Nalmefene has been promoted heavily in primary care, having been licensed in 2013 for the treatment of alcohol dependence under unusually specific conditions (see Box 1) [14]. It was recommended by the National Institute for Health and Care Excellence (NICE)

in late 2014 [15], and has been controversial [16–20]. The NICE appraisal committee stated that 'the exact magnitude of effect [of nalmefene] was uncertain' because of 'post hoc subgroup analyses' in trials 'not powered for these analyses' ([15], pp. 26–7). A recently completed systematic review concluded that 'the value of nalmefene for treatment of alcohol addiction is not established. At best, nalmefene has limited efficacy in reducing alcohol consumption' [21]. We explore the uncertainties in the available evidence, their regulatory handling and vested interests involved in order to better appreciate the issues and dilemmas arising.

Box 1 Marketing authorization for nalmefene [14].
Nalmefene is authorized for reducing alcohol consumption:

1 in people with alcohol dependence;
2 who have a high drinking risk level (defined as alcohol consumption of more than 60 g (7.5 UK units) per day for men and more than 40 g (5 UK units) per day for women, according to the World Health Organization's drinking risk levels);
3 without physical withdrawal symptoms, and who do not require immediate detoxification;
4 it should be initiated only in patients who continue to have a high drinking risk level 2 weeks after initial assessment; and
5 only used in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

THE TRIALS EVIDENCE BASE

We identified published studies on nalmefene through a systematic search (Box 2), alongside documents from the NICE appraisal [15,22–24], the European Medicines Agency (EMA) [14,25] and public trial registries [26–31]. Nalmefene has been the subject of six published trials, primarily with people who are alcohol-dependent (Table 1). These trials varied in treatment goals, nalmefene dose and regimen, and the kinds of psychosocial support provided with treatment (Table 1). The EMA assessment of nalmefene ([25], p. 28) was based primarily on three Lundbeck-sponsored trials: Esense 1 [35,36], Esense 2 [36,37] and Sense [38]. Two of the three other published trials [33,34], along with three unpublished trials (Table 2), were cited as supporting the choice of dose only ([25], p. 27). The NICE appraisal committee assessed data from the three Lundbeck trials because 'post-hoc analyses' of these studies formed the basis of the licensed population in the marketing authorization for nalmefene ([24], p. 26).

The Lundbeck trials (Table 1) were undertaken together across Europe in 19 countries between 2008/09

Box 2 Search strategy.
Searches were made on 13 June 2014, supplemented by a repeat search on 4 December 2014 to update our database in the following:

- PubMed
- Cinahl via EBSCOHost
- HealthSource via EBSCOHost
- Web of Science Core Collection
- Google Scholar (UK)

Example search strategy (PubMed)

#	Query
8	#4 OR #7
7	#5 AND #6
6	pubstatusaheadofprint OR (2013:2014[edat] OR 2013:2014[crdt] OR 2013:2014[dp])
5	alcohol* AND (nalmefene* OR selincro)
4	#3 AND Humans[Mesh]
3	#1 AND #2
2	Nalmefene OR Selincro OR nalmetrene
1	('Alcohol Abstinence'[Mesh] OR 'Alcohol Deterrents'[Mesh] OR 'Alcohol Drinking'[Mesh] OR 'Alcoholic Beverages'[Mesh] OR 'Alcoholic Intoxication'[Mesh] OR 'Alcoholics'[Mesh] OR 'Alcohol-Induced Disorders'[Mesh] OR 'Alcoholism'[Mesh] OR 'Alcohol-Related Disorders'[Mesh] OR 'Binge Drinking'[Mesh]) OR alcohol*[TiAb]

Searches were made in the following online trials registers on 3 December 2014 using the terms: Nalmefene OR Selincro

- ClinicalTrials.gov
- European Union Clinical Trials Register
- International Standard Randomised Controlled Trial Number register
- World Health Organization International Clinical Trials Registry Platform

Results

$n = 167$ records identified by database searches on 13.6.14 (dates: inception to 13.6.14)$n = 53$ records identified by database searches on 4.12.14 (dates: 1.6.14–4.12.14)$n = 8$ records identified by reference chasing

Minus duplicates, a total of $n = 202$ discrete records were identified using the strategy above. Excluding those clearly not relevant to nalmefene for alcohol problems from title and abstract [58]; 144 journal articles, reports and conference abstracts were examined.

From these eight full papers [32–39] reporting from six trials and one pilot trial of nalmefene for alcohol consumption and 31 conference abstracts related to the same seven trials of nalmefene (30 relating to the Esense 1, Esense 2 and Sense trials; 1 relating to the Anton trial) were identified.

Table 1 Summary of trial data.

Citation, year	*Study population*[a]	*Regimen & comparison*	*Country & setting*	*Primary outcomes*	*Reported findings*	*Funders*
Mason 1999 [32][b]	105 adults with alcohol dependence out-patients recruited through advertisements and press releases	12 w of twice-daily 10 mg/40 mg nalmefene or placebo (total daily 20 mg/80 mg/placebo)	USA (Florida) Single site: alcohol disorders research clinic	(a) Rate of relapse to heavy drinking; (b) percentage of days abstinent; (c) standard drinks per drinking day; All measured over the 12-w treatment period	Effect on 1 of 3 outcomes: fewer nalmefene patients (37%) relapsed to heavy drinking compared with placebo (58.8%) ($P = 0.02$)	Funded by NIAAA; drug and placebo provided by IVAX Corporation
Anton, 2004 [33]	70 adults with alcohol dependence recruited through clinical referrals and advertisements	12 w of daily 5 mg/20 mg/ 40 mg nalmefene or placebo; both with 4 sessions of motivational enhancement therapy	USA (11 States) 13 sites: mainly university medical/research centres	Heavy drinking days per month	No statistically significant difference between groups	Sponsored by Biotie, supported by Biotie statistician, Biotie were on study monitoring team and assisted in preparation of manuscript
Karhuvaara 2007 [34]	403 adults who had difficulty in controlling drinking with at least 18 heavy drinking days and no more than 14 consecutive abstinent days during the previous 12 w, recruited mainly through newspaper advertisements	28 w of 20 mg nalmefene/ placebo taken as needed[c]; after 2 w, the dose could be doubled or halved by investigators with some elements of BRENDA[d]	Finland 15 sites: 5 specialist treatment clinics; 6 private GP offices; 2 occupational health-care offices; 2 clinical research sites	Heavy drinking days per month	The nalmefene group had fewer heavy drinking days during the 28 w of treatment than the placebo group (final month 8.8 versus 10.6, $P = 0.0065$)	Study funded by Biotie and sponsor involved at all stages
Esense 1 [35,36]	604 adults with alcohol dependence, recruited from in and out-patient clinics including from advertisements	24 w of 18 mg of nalmefene or placebo to be taken 'as needed', both with 10 sessions of BRENDA[d]	39 sites: 4 in Austria, 11 in Finland, 16 in Germany and 8 in Sweden. Detailed descriptions of the study sites not reported	At trial registration[e]: 'Change from baseline in monthly number of heavy drinking days; Change from baseline in the total alcohol consumption (time-frame: 24 w)'	Effect on both outcomes[f]: nalmefene group had 2.3 fewer heavy drinking days per month, (95% CI = 3.8 to –0.8, $P = 0.0021$) and 11.0 g/day less alcohol (95% CI = 16.8 to –5.1) compared with placebo	Lundbeck sponsored the trials and was involved in the study design, data collection, data analysis, data interpretation and in providing medical writing assistance

(*Continues*)

Table 1. (Continued)

Citation, year	*Study population*[a]	*Regimen & comparison*	*Country & setting*	*Primary outcomes*	*Reported findings*	*Funders*
Esense 2 [36,37]	718 adults with alcohol dependence, recruited from both in-patient and out-patient clinics, including by advertisements	24 w of 18 mg of nalmefene or placebo to be taken as needed both with 10 sessions of BRENDA[d]	57 sites: 7 in Belgium, 3 in the Czech Republic, 16 in France, 10 in Italy, 7 in Poland, 4 in Portugal and 10 in Spain. Detailed descriptions of the study sites not reported	At trial registration[e]: 'Change from baseline in monthly number of heavy drinking days. Change from baseline in the total alcohol consumption. (time-frame: 24 w)'	Effects on 1 of 2 outcomes[f]: nalmefene group had 1.7 fewer heavy drinking days per month compared with placebo (95% CI = −3.1 to −0.4, $P = 0.012$).	As for Esense 1
Sense [38]	675 adults with alcohol dependence, recruited from out-patient clinics, including by advertisements	52 w of 18 mg of nalmefene or placebo to be taken as needed both with 10 sessions of BRENDA[d]	60 sites: 5 in the Czech Republic, 5 in Estonia, 2 in Hungary, 4 in Latvia, 2 in Lithuania, 15 in Poland, 8 in Russia, 4 in Slovakia, 10 in Ukraine and 5 in the UK	At trial registration[e]: 'Safety is measured by adverse events, clinical safety laboratory tests, vital signs, weight, body mass index, electrocardiograms, profile of moods states and physical examination [time-frame: 52 w]'	Paper does not report all as registered and refers to the two Esense outcomes as the co-primary implying no others. No effect of nalmefene was found for either consumption variable after 6 months; at 52 w the nalmefene group had 1.6 fewer heavy drinking days per month (95% CI = −2.9 to −0.3, $P = 0.017$) and 6.5 g less alcohol per day in the last month (95% CI = −12.5 to −0.4, $P = 0.036$)[f]	As for Esense 1 & 2

[a]Further details on inclusion and exclusion criteria are available in cited trial papers. [b]This trial was informed by an earlier pilot trial with 21 patients [39]. [c]'As needed': to be taken 1–2 h before any intake of alcohol, only when 'drinking seemed imminent' or 'a risk of drinking alcohol was perceived'. [d]BRENDA is a psychosocial intervention consisting of the following six components: (1) biopsychosocial evaluation; (2) report to the patient on assessment; (3) empathic understanding of the patient's situation; (4) needs identified collaboratively by the patient and treatment provider; (5) direct advice to the patient on how to meet those needs; (6) assess reaction of the patient to advice and adjust as necessary for best care [40]. In the Esense 1&2 and Sense trials, sessions of BRENDA were: 'approximately 15 to 30 m (except for the first session, administered at randomisation, which was approximately 30 to 40 m)' ([25], p. 29). [e]See body of text for discussion of deficits in pre-specification of outcome measures in trial registers. [f]These figures are for the original study population, not the unplanned subgroup analysis. NIAAA = National Institute on Alcohol Abuse and Alcoholism; CI = confidence interval.

Table 2 Available information on unpublished clinical trials.

Trial code	*Patient population*[a]	*Regimen & comparison*[a]	*Country*	*Outcome information*[a]	*Funders*
CPH-101-0701	166 patients who 'had a desire to reduce and gain better control of alcohol consumption and difficulties in controlling drinking plus a family history of alcohol problems' including some with dependence	28 w of flexible dose 10/20/40 mg nalmefene or placebo taken 'as-needed'[b] both with 'biopsychosocial assessment feedback and advice'	UK	Primary outcome: 'Monthly number of HDD' (heavy drinking days) '75% premature discontinuation for nalmefene; 68% for placebo'	Biotie
CPH-101-0399	150 patients who had 'difficulties in controlling drinking', including some with dependence	16 w of fixed daily dosing 10/40 mg/placebo	Finland	Primary outcome: 'Monthly number of HDD'	Biotie
CPH-101-0400	60 patients who had 'difficulties in controlling drinking' including some with dependence	52-w open-label, 10/20/40 mg flexible dosing, 'as-needed', uncontrolled study	Finland	Primary outcome: 'Monthly number of HDD'	Biotie

[a]Information summarized or quoted (as indicated) from manufacturer's response to request for clarification from NICE [22], pp. 14 and 16, and EMA Assessment report [25], p. 27. Additional information is redacted in the former and no other data, including outcome data, are available publicly. [b]No information on the meaning of 'as-needed' in these trials is available publicly. HDD: heavy drinking days.

and 2010/11, and published in 2013/14. Limited information is available on the 149 trial sites, which appear predominantly to include specialist treatment clinics and contract research organizations. Distributions of trial participants by site and recruitment method (advertisements, existing clinic patients, referral) are not reported.

Esense 1 was published first with effects favouring nalmefene (see Table 1), although differential dropout rates (53% for nalmefene versus 31% for placebo) were caused by adverse events in the nalmefene group [35]. In Esense 2 [37], a trial of identical design to Esense 1 [23], dropout rates were approximately 41 and 38%. There are reported reductions of approximately 65 and 60% in both alcohol consumption outcome measures for the nalmefene group and placebo groups, respectively, in Esense 2; an effect favouring nalmefene was reported for one of the two measures (see Table 1) [37].

Thirty-three per cent of patients in the Esense 2 trial were reported to have reduced their drinking during the assessment period prior to randomization [37]. Unplanned *post-hoc* analyses of data excluded these patients, and then statistically significant effects on both primary outcomes were reported for the remaining 'sub-group' [37]. A further 2013 report pooled this 'sub-group' data from both Esense 1 and 2 trials; at 6 months, the pooled nalmefene subgroup had 3.2 [95% confidence interval (CI) = –4.8 to –1.6, $P < 0.0001$] fewer heavy drinking days per month and 14.3 g (95% CI: –20.8 to –7.8, $P < 0.0001$) per day lower alcohol consumption compared with the pooled placebo subgroup [36].

The Sense trial [38] had a different design to the Esense trials, including a 1-year treatment duration and different primary outcomes at initial registration (Table 3). Attrition in Sense was again high, at approximately 35% in both arms. There were no effects on efficacy outcomes at 6 months; however, effects were reported at 12 months [38]. As for Esense 2 above, a *post-hoc* subgroup analysis was conducted which excluded participants who reduced their drinking during the assessment period prior to randomization. This analysis reported effects on both drinking outcomes after both 6 and 12 months [38]. There were no differences in serious adverse events between nalmefene and placebo groups, although the most common treatment-emergent adverse events such as nausea, insomnia, dizziness, vomiting, fatigue and decreased appetite were approximately twice as common in the nalmefene group, similar to the Esense trials.

WEAKNESSES IN THE EVIDENCE BASE

Trial outcome measures were not pre-specified fully at the outset

Clinical trial protocols should be registered publicly [41,42], with all outcome measures and associated timeframes specified fully to prevent selective reporting of favourable outcomes and unacknowledged changes to pre-specified measures [43,44]. The Lundbeck trials were registered at www.clinicaltrials.gov [26–28] and www.clinicaltrialsregister.eu [29–31] prior to commencement. Amendments to the registered protocols on www.

Table 3 Amendments to primary outcome measures [26–28].

Trial	*Original primary outcomes*	*Amendment details*
SENSE (NCT00811941) completed November 2010	18 December 2008: 'Measure: Safety is measured by adverse events, clinical safety laboratory tests, vital signs, weight, body mass index, electrocardiograms, profile of moods states and physical examination Time-frame: 52 w Safety issue? Yes'	**Amended 9 August 2011 to**: 'Measure: to evaluate the long-term safety and tolerability of as needed use of 20 mg nalmefene versus placebo using parameters such as adverse events, clinical safety laboratory tests and vital signs Time-frame: baseline to 52 w Safety issue? Yes Measure: to evaluate the effect of as needed use of 20 mg nalmefene on alcohol consumption by the monthly number of heavy drinking days (HDD) Time-frame: baseline to 24 w Safety issue? No Measure: to evaluate the effect of as-needed use of 20 mg nalmefene on the monthly total consumption Time-frame: baseline to 24 w Safety issue? No' **Amended 6 August 2013 to**: 'Measure: number of patients with adverse events (AEs) Time-frame: serious adverse events: 52 w and a safety follow-up (visit/telephone call) scheduled for 4 w after completion of the study or after withdrawal from the study. Other adverse events: 52 w Safety issue? Yes Description: overview of AEs Measure: percentage of patients who withdrew due to intolerance to treatment Time-frame: baseline to w 52 Safety issue? Yes Measure: change from baseline in the monthly number of HDD Time-frame: baseline and month 6 Safety issue? No Description: number of HDD over a month (28 days), where one HDD was defined as a day with alcohol consumption ≥60 g for men and ≥40 g for women. Measure: change from baseline in the monthly total alcohol consumption (TAC) Time-frame: baseline and month 6 Safety issue? No Description: TAC was defined as mean daily alcohol consumption in g/day over a month (28 days)
ESENSE 1 (NCT00811720) completed November 2010 ESENSE 2 (NCT00812461) completed April 2011	Esense 1: 18 December 2008 Esense 2: 21 December 2008 Measure: change from baseline in the monthly number of heavy drinking days; change from baseline in the total alcohol consumption Time-frame: 24 w Safety issue? No'	**Esense 1 and 2 amended 8 July 2013 to**: 'Measure: change from baseline in the monthly number of HDD Time-frame: baseline and month 6 Safety issue? No Description: number of HDD over a month (28 days), where one HDD was defined as a day with alcohol consumption ≥ 60 g for men and ≥ 40 g for women. Measure: change from baseline in the monthly total alcohol consumption (TAC) Time-frame: baseline and month 6 Safety issue? No Description: TAC was defined as mean daily alcohol consumption in g/day over a month (28 days)

clinicaltrials.gov show that the efficacy outcomes reported (as above) for the Sense trial [28] were added as primary outcomes only after trial completion (Table 3). Registered primary outcome measures for the Esense trials were also altered after the papers were accepted formally for publication, when definitions of 'heavy drinking days' and 'total alcohol consumption' were added (Table 3). The European Union (EU) register does not show trial amendment histories.

Licensing was based on *post-hoc* sample refinement

The licensing of nalmefene and its indication for a very specific population (Box 1) are based on efficacy data from the unplanned subgroup analyses described above, thus departing from the intention-to-treat principle [45]. Subgroup analyses normally involve pre-specifying levels of a baseline variable under investigation and testing for an interaction between the treatment and those levels, usually with a stricter level of significance [46]. What was conducted in the nalmefene trials could be described more accurately as *post-hoc* sample refinement. The information provided concerning the assessment procedures and the resulting data is not possible to evaluate in the published reports. The deleterious effects of sample refinement at study entry are well established in this field, and more broadly [47]. *Post-hoc* sample refinement should not be regarded as anything other than hypothesis-generating.

Sensitivity analyses do not provide consistent support for any effect

The NICE Evidence Review Group (ERG) noted the 'high dropout rates in the three nalmefene studies' ([24], p. 66). All randomised participants should be included in fully pre-specified [48] sensitivity analyses, even if lost to follow-up [49]. Such analyses were not identified in the publicly registered data [26–31]. A range of sensitivity analyses was performed none the less, of which multiple imputation (MI) is considered the least biased [50]. MI was performed in each Esense study for the two primary outcomes in both the total and subgroup populations; only one of four tests in each indicates a treatment effect (at $P < 0.05$) for nalmefene, and no others come close to statistical significance [23,35–37]. The systematic review by Palpaceur and colleagues [21] used baseline observation carried forward and found no evidence of benefit in sensitivity analyses. Six members of the EMA committee considering nalmefene signed a 'Divergent Position' statement, highlighting concerns about efficacy in light of the sensitivity analyses and the small effect size ([25], p. 73).

Appropriate comparisons, external validity and cost-effectiveness issues

The Declaration of Helsinki states that new interventions must be tested against the best current proven intervention, and cautions against abuse of placebo-controlled studies [51]. In individuals with mild dependence who have not responded to psychological intervention or who request pharmacotherapy, naltrexone (a generic drug), in conjunction with psychological treatment, is recommended by NICE for reducing drinking [52], potentially making this a reasonable comparator. Although placebo comparisons have scientific merits, and indeed are required by the US Food and Drug Administration in these types of studies, non-inferiority designs may also be appropriate, depending on the precise hypotheses being tested and the validity of the comparisons being made. Placebo run-in periods do not influence the effects of naltrexone [53], and placebo effect sizes in alcohol treatment trials have been growing over time for reasons which are not understood [54]. This appears to be an important target for study, and the construct of research participation effects [55,56] may be useful in future.

Investigators on the Lundbeck trials refer to the 'different biochemical profile' of nalmefene and naltrexone [57]; however, differences in *in-vitro* receptor actions cannot be assumed to be clinically important [58]. Although naltrexone is associated with a risk of hepatotoxicity at very high doses (>300 mg/day), it is considered 'very unlikely' with doses of 25–50 mg per day ([52], p. 417); the risk is so low that routine liver function test monitoring is not recommended [52]. Thus, the clinical significance of any difference between the two drugs is unclear. The Institute for Quality and Efficiency in Healthcare (the German equivalent of NICE) concluded that any added benefit of nalmefene over naltrexone is unproven [59]. The lack of comparative effectiveness data prevented the NICE ERG from commenting on the relative cost-effectiveness of nalmefene and naltrexone [24]. Even if naltrexone plus psychosocial support is not widely used, as the NICE appraisal committee was informed ([15], p. 27), naltrexone is a very similar, much cheaper drug. There is also good evidence for acamprosate [60,61] and accumulating evidence for topiramate, both also generic drugs [62].

No data are available on the adequacy of the psychosocial intervention 'BRENDA' [40] used in both arms in the Lundbeck trials. NICE guidelines [52] recommend more intensive psychosocial support over 12 weekly sessions (of cognitive–behavioural therapy, for example) in harmful drinking and mild dependence before pharmacotherapy is considered. A more intensive psychosocial intervention than BRENDA would also therefore seem an appropriate comparator, and there is a range of possible uses and combinations of medication and psychosocial interventions

that could merit evaluation within more patient-centred approaches to care [63]. The NICE ERG reported that 'it believes it probable that delayed [nalmefene] treatment reserved for those who do not respond' to this optimal support 'is more cost-effective than immediate treatment for all patients' ([24], p. 118). The one published clinical trial which used a more strongly evidence-based psychosocial intervention (motivational enhancement therapy) found no added benefit of nalmefene [33].

DILEMMAS FOR PRACTICE AND SERVICE COMMISSIONING

Nalmefene has not been tested in free-to-access primary care (in one of the early trials in Finland some participants attended private general practices after responding to advertisements [34]), so generalizability to UK primary care, and similar routine practice contexts, is unknown. The NICE technology appraisal committee did not recommend a setting for prescribing nalmefene, as such recommendations are 'outside the scope of a technology appraisal' ([15], p. 24). In the cost–effectiveness model provided by Lundbeck, 75% of prescribing is assumed to take place in primary care ([23], p. 218), and it has been promoted heavily there [64,65]. In both arms of the Lundbeck trials, the 'BRENDA' psychosocial support consisted of an initial 30–40m session followed by fortnightly and later monthly 15–30m sessions ([25], pp. 29–31), there have been long-standing implementation problems in primary care with much briefer interventions [66,67]. The specific subgroup for whom nalmefene is licensed may not be easy for clinicians to identify correctly (Box 1), and it is unclear how psychosocial support will be provided and resourced in practice. These issues also give rise to dilemmas for commissioners of services.

Proponents of nalmefene argue that it should be used widely and proactively for public health benefit [68]; however, uncertainties about efficacy, effectiveness and cost-effectiveness of nalmefene inhibit appraisal of the possibility of such benefits. As with naltrexone [69], the evidence suggests that any reduction in consumption may not persist much beyond the period when nalmefene is taken [34].

The low level of confidence possible in existing data poses dilemmas for policy and practice which are not easy to resolve. Those who look to the peer-reviewed literature may be impressed by the variety of publications favourable to nalmefene. However, many such pieces are authored or co-authored by those involved in the Lundbeck trials, in receipt of Lundbeck funding or who are company employees [68,70–82]. Others interested in the drug may access Lundbeck literature, such as the Selincro® website for health professionals, which emphasises absolute rather than relative reductions in consumption among those receiving nalmefene [83].

IS THE REGULATORY SYSTEM STRONG ENOUGH TO HANDLE WEAK EVIDENCE?

Important weaknesses in nalmefene trial registration, design, analysis and reporting hamper efforts to understand if and how it can contribute to treating alcohol problems in general practice or elsewhere. The efficacy of nalmefene appears uncertain; a judgement of possible limited efficacy in an unusually defined and highly specific *post-hoc* subgroup should not provide the basis for licensing or recommending a drug.

The EMA has been subject to criticism about its handling of conflicts of interests regarding the pharmaceutical industry [84] and inconsistencies in its approach to the issue of active controls in trials [85]. In a UK Parliamentary Health Committee enquiry into the influence of the pharmaceutical industry, NICE acknowledged that its relationship with industry 'is one in which some degree of conflict is inevitable' ([5], p. 90) and concerns exist regarding industry influence in health technology assessment more widely [2,86]. There is ample guidance to ensure that clinical trial findings are reliable, but that does not prevent such guidance being ignored. The unusual nature of the evidence base available for nalmefene, and the regulatory handling of the uncertainties therein, raise difficult questions about the regulatory systems involved and the consequences arising for healthcare resource use and patient care.

IMPLICATIONS FOR ADDICTION SCIENCE

The evidence presented on nalmefene should be understood in the wider context of alcohol treatment trials [10,12]. This suggests that the existing modest effect sizes for nalmefene [21] may reduce with further study, as has been observed for other drugs [53,87]. Independently conducted research is needed on medications for alcohol treatment, including cost–effectiveness studies and further trials in the settings in which such treatments are used or promoted. Further development of the evidence on psychosocial approaches may be even more important.

Study of funding effects has not been well developed in the addiction field [88], despite the long-standing wider recognition of the need for such study [89]. Such study should be informed appropriately by existing evidence, taking care not to make unwarranted assumptions. This investigation makes clear the need to study the involvement of the pharmaceutical industry in alcohol treatment trials and the resulting implications for the literature. Pharmaceutical companies, including Lundbeck, are involved in the Alcohol Clinical Trials Initiative, which aims to improve the evidence base [10]. Effective management of vested interests may be needed to achieve that aim, and it is important to study the extent to which this is achieved.

Alcohol problems are complex, and require evidence unbiased by vested interests.

Declaration of interests

The authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Ethics statement

Ethical approval was not required for this paper.

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